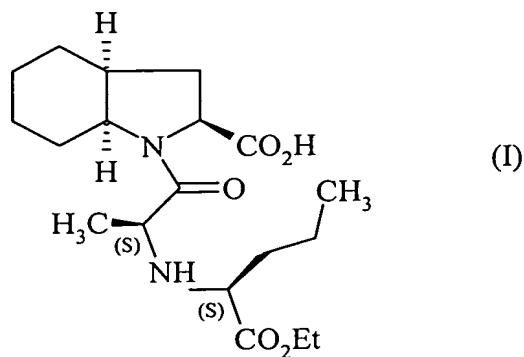


**NEW PROCESS FOR THE SYNTHESIS OF PERINDOPRIL
AND ITS PHARMACEUTICALLY ACCEPTABLE SALTS**

The present invention relates to a process for the synthesis of perindopril of formula (I) :



and its pharmaceutically acceptable salts.

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-
5 butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive
10 peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

15 In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity starting from reasonably priced starting materials.

Patent specification EP 0 308 341 describes the synthesis of perindopril by the peptide-type coupling of (2S,3aS,7aS)-octahydroindole-2-carboxylic acid benzyl ester with N-[(S)-1-carboxybutyl]-(S)-alanine ethyl ester, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

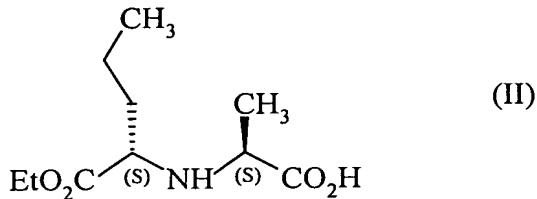
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That process has the advantage of yielding perindopril in a good yield from starting materials for which industrial synthesis has already been described.

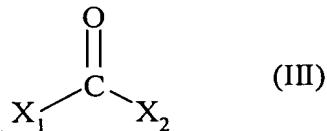
However, it also has drawbacks associated with the use of dicyclohexylcarbodiimide in the coupling step : the formation of coupling impurities, and of dicyclohexylurea, a by-product
10 which is difficult to remove.

The Applicant has now developed a new process for the synthesis of perindopril that avoids the formation of those secondary products.

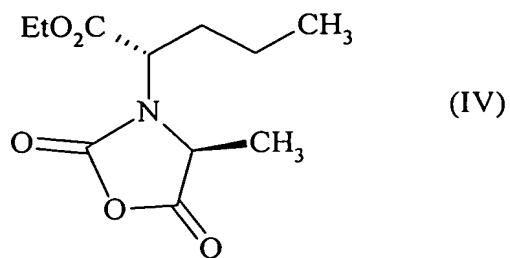
15 More specifically, the present invention relates to a process for the synthesis of perindopril and its pharmaceutically acceptable salts which is characterised in that the compound of formula (II) :



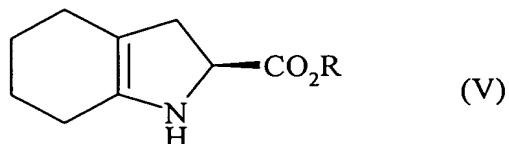
is reacted with a compound of formula (III) :



25 wherein X₁ and X₂, which may be identical or different, each represents a leaving group, to yield the compound of formula (IV) :



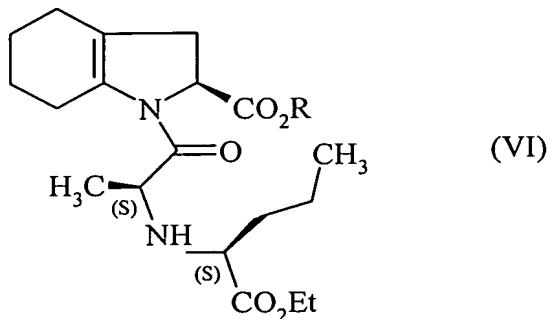
which is reacted with a compound of formula (V) :



wherein R represents a hydrogen atom or a benzyl or linear or branched ($\text{C}_1\text{-C}_6$)alkyl group,

5

or an addition salt thereof with a mineral or organic acid,
to yield, after isolation, a compound of formula (VI) :



wherein R is as defined hereinbefore,

10 which is hydrogenated in the presence of a catalyst such as, for example, palladium, platinum, rhodium or nickel,
under a hydrogen pressure of from 1 to 30 bars, preferably from 1 to 10 bars, to yield, after deprotection where necessary of the acid function, perindopril of formula (I) which is converted, if desired, to a pharmaceutically acceptable salt such as the tert-butylamine salt.

Appropriate leaving groups X_1 and X_2 that may be mentioned, without implying any limitation, include the halogen atoms and the groups tosylate, mesylate, linear or branched (C_1 - C_6)alkoxy, linear or branched (C_1 - C_6)alkylthio, imidazolyl, benzimidazolyl, tetrazolyl, benzotetrazolyl, linear or branched trihalo-(C_1 - C_6)alkyl, linear or branched trihalo-(C_1 - C_6)alkoxy, and succinimidylxyloxy.

Preferred leaving groups X_1 and X_2 that may be mentioned include the chlorine atom and the imidazolyl and trichloromethoxy groups.

The Example below illustrates the invention but does not limit it in any way.

EXAMPLE : (2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]-propionyl}octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

Step A : Ethyl (2S)-2-[(4S)-4-methyl-2,5-dioxo-1,3-oxazolidin-3-yl]pentanoate

5 Introduce into a reactor, at 0°C, 200 g of N-[(S)-ethoxycarbonyl-1-butyl]-(S)-alanine, 1.5 litres of toluene, and then 184 g of 1,1'-carbonyldiimidazole, then bring the temperature of the reaction mixture to 20°C. After stirring for 1 hour at 20°C, cool the mixture to 0°C again, filter off the precipitate obtained, then evaporate the filtrate to yield the title product in a yield of 90 %.

10

Step B : (2S)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid

Introduce 200 g of (2S)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylic acid and 1.5 litres of dichloromethane into a reactor, followed by 180 ml of triethylamine.

15

Subsequently, slowly add a solution of 290 g of the compound obtained in the above Step in 500 ml of dichloromethane and then stir for a further 1 hour at ambient temperature. After the addition of water, the reaction mixture is cooled to 15°C and the pH is adjusted to 4.2 by the addition of a 2N hydrochloric acid solution. Following extraction, the organic phases are washed and then evaporated to yield the expected product.

Step C : *(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-octahydro-1H-indole-2-carboxylic acid*

Introduce into a hydrogenation vessel 200 g of the compound obtained in the above Step in solution in acetic acid, and then 5 g of 10 % Pt/C. Hydrogenate under a pressure of 5 bars at ambient temperature until the theoretical amount of hydrogen has been absorbed.

5 Remove the catalyst by filtration, and then cool to from 0 to 5°C and recover, by means of filtration, the solid obtained. Wash the cake and dry it to constant weight.

Step D : *(2S,3aS,7aS)-1-{(2S)-2-[(1S)-1-(Ethoxycarbonyl)butylamino]propionyl}-octahydro-1H-indole-2-carboxylic acid tert-butylamine salt*

10 The compound obtained in the above Step (200 g) is dissolved in 2.8 litres of ethyl acetate, and then 40 g of tert-butylamine and 0.4 litre of ethyl acetate are added.

The suspension obtained is then refluxed until complete dissolution occurs, and the solution obtained is then filtered in the heated state, and cooled, with stirring, to a temperature of from 15 to 20°C.

15 The precipitate obtained is subsequently filtered off, made into a paste again with ethyl acetate, dried and then crushed to yield the expected product in a yield of 95 %.